Providing Chlamydia Screening and Treatment to Pregnancy Women to Prevent Adverse Pregnancy Outcomes: A Randomized Control Trial

NCT number NCT03862495
Document Date 02/12/2018

Providing Chlamydia Screening and Treatment to Pregnancy Women to Prevent Adverse Pregnancy Outcomes: A Randomized Control Trial

Dermatology Hospital, Southern Medical University,

Guangdong Provincial STD Research and Innovation Center

UNC-South China STD Research and Training Center

University of North Carolina Project-China

Version 1.0 (February 12, 2018)

Contents

Contents

I. Background

Chlamydia trachomatis (henceforth referred to as C. trachomatis), is not only one of the most common sexually transmitted diseases, but also a global public health crisis. It is estimated, that every year the number of new Chlamydia cases exceeds 100 million worldwide[1]. Since the 1990's in North America, Northern Europe, and other developed nations, chlamydial infections have presented long-term trends[2 3]. Due to physiological sex differences, the number of infected women is significantly higher than infected men. Additionally, up to 70-95% of women infected with chlamydia are often clinically asymptomatic[4]. In women infected with chlamydia for long periods of time without proper treatment, the infection may spread to the cervix and fallopian tubes, which could lead to pelvic inflammatory disease, tubal factor infertility and other adverse reproductive outcomes.

The prevalence of Chlamydia in pregnant women is also high. In Africa, the prevalence of pregnant women infected with Chlamydia fluctuates between 0-30%. In Asia, the prevalence is as high as 41-44% in some countries[5]. Some studies have shown that chlamydia infection during pregnancy is associated with adverse outcomes such as ectopic pregnancy, miscarriage, stillbirth, premature birth, pre-labor rupture of membranes (PROM), low infant birth weight (LBW) and others. A previously conducted meta-analysis (mostly non-experimental studies) also suggests a significant correlation between chlamydial infection in pregnant women and miscarriage, stillbirth, premature birth, and ectopic pregnancy (unpublished). A few individual intervention studies have shown that regular chlamydia screening and treatment in pregnant women can reduce the incidence of LBW, PROM, and increase perinatal survival[6]. However, these studies were not randomized control trials (RCT). One RCT study examined the treatment effect of erythromycin on Chlamydia infected women with premature and low birth weight

children, showing no difference in the overall effect between the erythromycin and the placebo[7] . A recent publication in The Lancet Infectious Diseases reported that there are no significant correlations between genital chlamydia infection and premature birth, small for gestational age, and stillbirth in a prospective cohort study[8 9]. Additionally, a review published in Cochrane by Brocklehurst and Rooney mentions that the probability of genital chlamydia causing severe conjunctivitis and neonatal pneumonia in newborns, via mother-to-child transmission, is 15-25% and 5-15%, respectively[10]. Currently, there is a lack of prospective randomized controlled trials that investigate the role of chlamydial infection screening and treatment in the prevention of adverse pregnancy and neonatal outcomes.

Although there is still debate within the international community on the cost-effectiveness of screening pregnant women for chlamydia, United States clinical guidelines recommend that pregnant women below the age of twenty-five, pregnant women twenty-five years/older but with behavioral risk factors should undergo chlamydia screening[11]. According to an Australian study, when the prevalence of Chlamydia in pregnant women is greater than 11%, the potential benefit from screening will be higher than the cost of screening itself.[12] A review published in 2002 further suggests that when the prevalence of women is between 3.1-10%, screening of chlamydia can be cost-effective[13]. Previous studies have found that the prevalence of chlamydia in pregnant women in China was between 4.9% -14.0%[5 14], indicating a serious Chlamydia epidemic. In 2015, the reported incidence of genital Chlamydia in China was 37.18 / 100,000. Guangdong province reported an incidence of 150.88 / 100,000, second highest among all provinces, autonomous regions, and municipalities throughout China. Additionally, the number of newly reported cases are increasing. In 2016, there were 65,988 newly reported cases. Concurrently, compared with other nations, the incidence of spontaneous abortion, premature

birth and low birth weight children in China is also high. In 2015, the incidence of spontaneous abortion in China was about 5-15%; preterm birth was 6.1% [15]; and low birth weight was 6.3%[15]. In 2015 alone, there were 122,300 reported stillbirths in China, the fourth highest in the world[16], indicating a need for significant improvement in perinatal and neonatal health. Additionally, in January 2016, China completely liberalized its second child policy, welcoming a small fertility peak in 2017. In 2017, Guangzhou also saw increased childbirth with permanent resident births (including census registered and non-native residents living in Guangzhou more than 6 months) reaching 126,000. These increased births may also increase the burden of maternal, fetal, and newborn diseases in China.

Despite the substantial burden of chlamydia and adverse pregnancy outcomes, no previous research has been conducted to examine the effects of genital chlamydia infection on adverse pregnancy outcomes in China. There is no clinical guideline on screening for genital Chlamydia infections in pregnant women. Therefore, it is important to understand the impact of genital Chlamydia in China through randomized controlled studies that explore the relationships between Chlamydial infection and adverse pregnancy outcomes, and the feasibility and effectiveness of screening and treatment. The purpose of this study is to 1.) clarify the causal relationship between genital C. trachomatis infection and adverse pregnancy outcomes and 2.) determine whether screening and treatment of genital C. trachomatis in pregnant women can reduce adverse pregnancy outcomes. The research team will screen pregnant women in Guangzhou for genital C. trachomatis to understand its prevalence. We will also conduct a randomized controlled trial to explore whether clinical treatment of C. trachomatis-positive patients can reduce adverse pregnancy outcomes, and neonatal chlamydial conjunctivitis and pneumonia. This study will have great scientific and social significance. Firstly, it will provide

an important reference for the formulation of public health policies, clinicians' treatment of chlamydia infection in pregnant women, and prevention of chlamydial infection in newborns. Secondly, it will be a valuable resource for the prevention of adverse pregnancy outcomes and neonatal infection associated with sexually transmitted diseases in other developing countries.

II. Purpose

1. To examine whether screening and treatment of genital C. trachomatis in pregnant women can reduce adverse pregnancy outcomes
2. To explore the effectiveness of screening and treatment of genital C. trachomatis in reducing mother-to-child transmission
3. To evaluate the cost-effectiveness of screening and treating chlamydial infections in pregnant women, and provide a basis for health policy decisions on how best to screen / treat

III. Hypotheses

1. Effective screening and treatment of pregnant women with genital C. trachomatis will reduce adverse pregnancy outcomes
2. Effective screening and treatment of pregnant women with genital C. trachomatis will reduce neonatal chlamydial conjunctivitis and pneumonia
3. C. trachomatis screening and treatment of pregnant women is cost-effective.

IV. Content

Target population and sampling

This study will recruit pregnant women from a maternal/child health hospital in Guangzhou city and county. Guangzhou Women and Children Medical Center and Zengcheng Maternal and

Child Health Hospital (now Zengcheng Hospital of Guangzhou Women and Children Medical Center) are two key hospitals for perinatal health and pregnant women. In 2016, Guangzhou Women and Children Medical Center delivered 22,455 infants, the highest delivery volume among the hospitals throughout the city. Additionally, Zengcheng Hospital of Guangzhou Women and Children Medical Center provides prenatal care, delivery care, and other main medical services for pregnant women in Zengcheng district. Given the rich clinical research resources and experience of both hospitals, we have elected to conduct our large-scale randomized controlled clinical trial at these two hospitals.

Inclusion criteria: 1) pregnant women on their first visit to the hospital (regardless of gestational age); 2) aged 18 or above; 3) agree to participate and sign an informed consent. Exclusion criteria: 1) systemic or topical vaginal antibiotics were used within 2 weeks prior to the first perinatal visit; 2) diagnosed adverse pregnancy outcomes at recruitment (e.g., stillbirth); 3) pregnant women who refuse to participate in this study.

Sample size estimation

The sample size calculation was based on the following assumptions: 1, the conservative estimate of prevalence of Chlamydia is around 6% among pregnant women in Guangzhou; 2, our meta-analysis showed that the odd ratio of adverse pregnancy outcomes in infected pregnant women versus non-infected pregnant women was 1.8; 3), assuming a 5% significance level on both sides, with a 80% efficacy test and a 2% loss- to-follow-up rate, in order to demonstrate a significantly lower incidence of adverse pregnancy outcomes in the intervention group than in the control group (estimated at 10%, from preliminary data, unpublished results), the sample size

should be approximately 7,725 for each group with an overall target sample size of 15,450 (when β = 0.8, the estimated sample size is 15,449).

Alpha	OR	p2	Power	# of positive samples	Prevalence (%)			Total sample size (include 2% loss-to-follow-up)		
0.05	1.8	0.1	0.9	995	5	6	8	20,306	16,922	12,691
0.05	1.8	0.1	0.8	757	5	6	8	15449	12874	9656

* The prevalence of abortion, stillbirth, premature birth, low birth weight, SGA and neonatal deaths was 10.1% in the same cohort recruited by Guangzhou Women's Center for 2012-2017.

Questionnaire and follow-up

We will obtain informed consent from participants. We will inform them of the main purpose of the study and the research process (Annex 1). We will emphasize that participation is completely voluntary. Refusal or withdrawal will not affect medical treatment and health care services at the Center. All information obtained by the research group will be strictly confidential and shall not be shared with any other third parties prior to obtaining consent from the participants. After enrolment, we will conduct a baseline survey with all participants, collect relevant medical history, information, and urine samples. The survey will be carried out by the research staff at the Center. The survey content will be built on the questionnaire that is developed by the birth cohort at the Center. We will obtain information on socio-demographic characteristics, chronic medical history, other acute conditions during the first trimester of pregnancy(diagnosis and treatment), number of pregnancies, prior history of previous caesarean section, history of recurrent miscarriage, prior

history of ectopic pregnancy, history of psychiatric illness (e.g., depression), smoking/drinking habits, and history of second-hand smoke exposure. We will add other questions to collect information about history of sexually transmitted diseases and gynecological diseases (such as cervical surgery), whether or not systemic or topical antibiotics were used within the past one month, drug use, sexual behaviors, sexual partner history both before and during pregnancy, history of falls during pregnancy, previous experience of domestic violence, etc. (Annex 2).

Participant recruitment and randomization

We will adopt the block randomization approach. Specific randomization steps include: 1) After we recruit participants, we will group the them into blocks on a chronological basis. Each block will have 20 women who be numbered sequentially. 2) We will then randomly divide them in each block into intervention and control groups. That is numbering the participants from 1 to 20, then generating 10 random numbers and the corresponding participants will be assigned to the intervention group. For participants in the intervention group, we will immediately test for C. trachomatis and Neisseria gonorrhoeae (See Figure 1 for the flowchart of the study design). Participants who test positive for either infection in the intervention group will be linked to physicians at the Center for treatment. For the control group, urine samples will be collected and tested immediately after childbirth or in the event of an adverse pregnancy outcome. In the event of a positive test result, the participant will be suggested to return to the Center for further treatment.

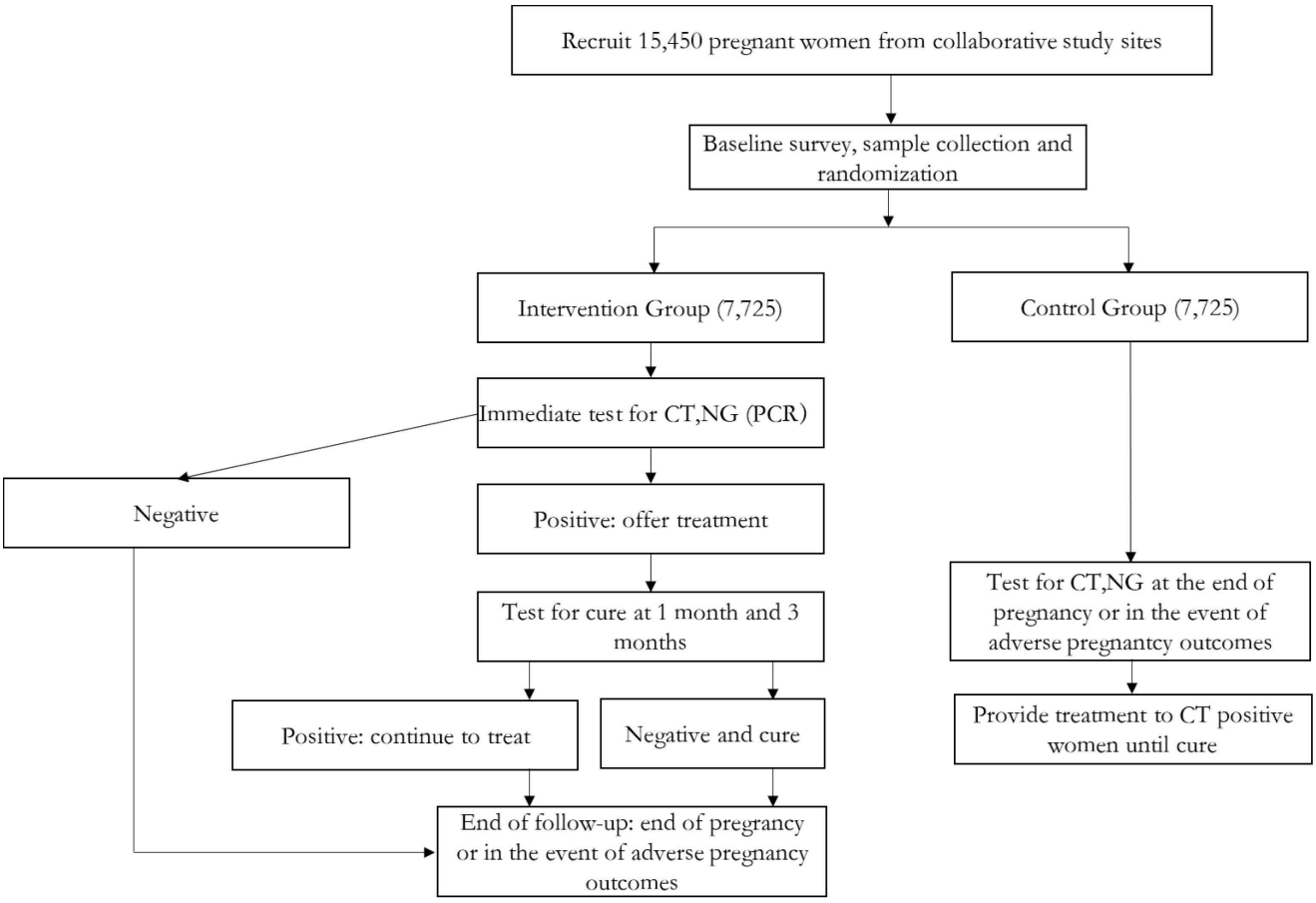

Figure 1, Flow Chart of the study.

Intervention and Treatment

This RCT will follow the principle of nonmaleficence. For pregnant women enrolled in the intervention group, after completing the test, laboratory personnel will inform the researchers of positive results. The sample number of the positive result will then be reported to the Guangzhou Women and Children Medical Center (GWCMC). The center's physicians will match the result to the correct patient and notify them of their results. We will provide a training session to the physicians at the Center about the national standard treatment plan (Azithromycin 1g, single oral administration). They will be suggested to treat patients according to the Chinese clinical and

prevention guidelines for sexually transmitted diseases, and final decision will be made by the physician and patient together. Physicians will ask patients to return to the women's center for test of cure and re-testing in one month and three months after treatment respectively. At each of these visits, we will collect urine samples for Chlamydia testing. Patients who still test positive will continue treatment until they test negative. Additionally, pregnant women who test positive for Chlamydia will also be suggested to bring Azithromycin home to treat their spouses. We will also caution them to avoid sexual activity during the treatment period (7-10 days starting from day of treatment). We will also provide consultation services for the participants to deal with intimate partner relationship under this circumstance.

For pregnant women enrolled in the control group, we will delay the urine sample collection and the test until after delivery, or in the event of adverse pregnancy outcomes. In the event of a positive test, the patients will be informed of the positive test results the same way as the intervention group. In the event of a positive test, physicians will be suggested to provide patients and their spouses with treatment identical to the intervention group. In the event of a negative test, there will be no need for treatment. Specific treatment options will be the same to the intervention group. Physicians will ask patients to return to the Center one month after treatment for test of cure. Endpoint of the study is defined as either the occurrence of an adverse pregnancy outcome or delivery of a newborn.

After delivery, all patients who tested positive will be informed of the risk of Chlamydia infection in neonates. About 1-week post-partum (including Caesarean newborns), neonatal conjunctival scrapings and nasopharyngeal/pharyngeal swabs will be collected. In addition, infants will be examined for neonatal conjunctivitis and / or pneumonia clinical symptoms (see details in secondary outcome). In the case of a confirmed diagnosis, treatment will be carried out.

If there is no confirmed diagnosis, family of the newborn will be advised to pay close attention for the emergence of signs of conjunctivitis and / or pneumonia, and promptly return to the hospital if the post-neonatal clinical symptoms appear. This study will follow the treatment guidelines for of the American Academy of Pediatrics Infectious Diseases and America Centers for Disease Control and Prevention for conjunctivitis and pneumonia: Erythromycin 12.5 mg/kg, oral, 4 times a day, for 14 days. For patients that do not return to the hospital for screening, the research team will call patients and verify the newborn infection status and whether treatment was provided at a different hospital.

Justifications of the control strategy

Currently in China, there are no clinical guidelines or policies that suggest routine genital chlamydia screening in pregnant women.[15] The clinical standards for conducting a chlamydia test in pregnant women include relevant symptoms including urethritis, cervicitis and occurrence of adverse pregnant outcomes.[15] Compared to current standard care (i.e., no routine screening and treatment), both our intervention (free screening for chlamydia at recruitment and linkage to care) and control (free screening for chlamydia at delivery of the baby and linkage to care) strategies provide better care to the target group.

Safety management plan

Criteria for withdrawal: if participants want to quit the study for any reasons; occurrence of any adverse pregnancy outcomes or recommendation by their personal physician to stop participation; Data and safety monitoring will be done by The Center and the Dermatology Hospital of Southern Medical University.

In addition, the study complies with the following statements: Any risk is the least possible for achieving the objectives of the research; Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate; No inducements, monetary or otherwise, will be offered to terminate a pregnancy; Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and Individuals engaged in the research will have no part in determining the viability of a neonate.

Primary Outcome

Our primary outcome is the occurrence of adverse pregnancy-related outcomes between the two groups, which include: 1) stillbirth (the definition of stillbirth in this study will use International Classification of Diseases (ICD-11)： death prior to complete expulsion (pregnant >=28 weeks) and death during extraction [17]); 2) Spontaneous abortion (less than 1000gms or less than 28 weeks); 3) Preterm labor (birth fewer than 37 weeks gestational age; Infants born before 28 weeks are considered very early-preterm; 28-32 weeks early-preterm; 32-37 weeks late-preterm. 4) Premature rupture of membranes (prior to onset of labor); 5) Low birth weight (2,499g or less); 6) Small for gestational age (weight below the 10th percentile); and 7) perinatal death.

Secondary Outcomes

The secondary outcomes include: C. trachomatis infection of the newborn, Chlamydial conjunctivitis, and pneumonia in the newborn. Laboratory methods for the diagnosis of neonatal

chlamydial infection include: 1) Detection of C. trachomatis by sampling from conjunctival scraps and nasopharyngeal/ pharyngeal posterior through direct fluorescence (DFA); 2) PCR and 3) chlamydia culture.

Common Chlamydia conjunctivitis clinical symptoms and supplementary examinations include eyelid and nasal congestion, or 2) catarrhal or mucopurulent secretions, occurring within 5-14 days after birth. It is possible for exudate adhesions to form pseudomembranes. If treatment is delayed more than two weeks, conjunctival follicles may also form.

Chlamydia pneumonia infection may appear insidiously. However, symptoms will usually appear in 4-12 weeks. Common clinical manifestations include nasal mucus secretion, nasal congestion, intermittent cough, shortness of breath, rales on auscultation. There is usually no fever or change sin consciousness. Laboratory examinations may show normal white count but elevated eosinophils; moderate hypoxemia on arterial blood gas; bilateral interstitial markings on chest radiography.

Clinical Data Collection

Maternal: 1) mode of delivery: vaginal delivery or caesarean section; 2) whether twins or not; 3)occurrence of complications of childbirth, such as fetal umbilical cord around the neck, dystocia, uterine rupture and amniotic fluid embolism; 4) occurrence of stillbirth, spontaneous abortion, or premature rupture of membranes; 5) development of fetus during prenatal period (occurrence of fetal malformations and types of malformations etc.); 6) history of chronic diseases during pregnancy, including gestational diabetes, hypertension, autoimmune diseases, etc.; 7) nutritional status of pregnant woman; 8) HIV and Syphilis test and treatment information for positive cases;

9)essential clinical data: chlamydia and gonorrhea test and treatment information; 10)other clinical information: general health information (height, weight, blood pressure, blood glucose, complete blood count, urine analysis).

Neonatal: 1) Information on birth weight, neonatal death etc.; 2) occurrence of any symptoms such as conjunctivitis, pneumonia, genital infections etc.

Urine collection and laboratory testing

1) Sample collection for pregnant women with Chlamydia trachomatis / gonococcal: We will collect urine samples for testing. Before collection, we will ensure that the patient has not urinated within the last 1 hour. The patient also should not clean the sampling site in advance, such as washing etc. Patients will be instructed to collect urine in a urine cup. Urine in the urine cup cannot remain at room temperature (2-30℃) longer than 24 hours. We will use flexible pipes from the Rochecobas® PCR Urine Sample Kit, to transfer urine to the storage tube (Roche cobas® PCR Media tube). After tightening the lid, storage tubes will be turned over up and down five times. Samples will be transferred to the Dermatology Hospital of Southern Medical University for testing.

2) Neonatal samples collection: We will collect eyelid swabs (sample needs to contain eyelid epithelial cells) and pharyngeal swabs. Samples will be maintained at 2-8°C and screened within 24 hours.

3) Chlamydia trachomatis / Neisseria gonorrhoeae test: Reagent: Roche Cobas CT / NG Test kit; Instrument: Roche Cobas Z480, Roche Cobas X4800. Detection principle: CT: detecting Chlamydia MOMP gene by FAM labeling probe; NG: detecting Neisseria gonorrhoeae DR-9

Variant gene by HEX labeling probe. The samples will be automatically extracted and loaded using the Roche X4800 and its processing reagents. The CT / NG will be detected by using the Roche Cobas Z480. The system will automatically interpret the positive and negative values.

4) Chlamydia genotyping

a. Sample Source: Chlamydia trachomatis positive / Neisseria gonorrhoeae positive urine samples

b. Extraction of Nucleic acid: Take 1 mL positive sample and centrifuge at 12000 rpm for 30 min. Discard the supernatant and add 50 μL of lysate (10 mmol / L Tris-HCl, 1 mmol / L EDTA, 0.5 mmol / L Tween-20, pH 8.3). Mix and boil the sample at 100 ℃ for 10 min, centrifuge at 12000 rpm for 10 min. Use the supernatant as PCR template.

c. Chlamydia nucleic acid amplification PCR: According to the literature [2, 3] synthesis of two pairs of primers, which the external is upstream 5'-ATGAAAAAACTCTTGAAATCGG-3 'and downstream 5'-TTTCTAGACTTCATTTTGTT-3'; amplified fragment of about 1.1kb. The internal primer sequence is upstream 5'-GGGAATCCTGCTGAACCAAG-3 'and downstream 5'-AATTGCAACGAAACGATTTG-3', and the amplified fragment is about 0.9kb (all the above primers are synthesized by Shanghai Bioengineering Co., Ltd.). PCR reaction system was 50 μL (ddH20, 36.5 μL, 10 μL PCR buffer 5 μL, dNTP 1 μL, external primer 2 μL, Taq DNA polymerase 0.5 μL); the reaction conditions include Pre-denaturate at 94 °C for 3 min; denaturation at 94 ° C for 30 s, Annealing at 55 ℃ for 30 s, extension at 72 ℃ for 40 s with 35 cycles in total; extension at 72 ℃ for 5 min. The amplified product

is purified and sequenced by Shanghai Bioengineering Co., Ltd. The sequencing primers are the same as the internal primers.

d. Sequencing Analysis: The following 10 types of Ct Omp1 sequences are used for BLAST analysis: B / M17342, D / X62920, E / X52577, F / X52080, G / AF063199, H / X16007, I / AF063200, J / AF063202, K / AF063204, Ja / AF063203. Sequence analysis is performed by using Bioedit and DNAStar molecular biology software.

5.) Chlamydia drug resistance gene test

a. Sample source: urine samples positive for Chlamydia trachomatis / Neisseria gonorrhoeae

b. Extraction of Nucleic acid: Take 1 mL positive sample and centrifuge at 12000 rpm for 30 min. Discard the supernatant and add 50 μL of lysate (10 mmol / L Tris-HCl, 1 mmol / L EDTA, 0.5 mmol / L Tween-20, pH 8.3) , mix and boil the sample at 100 ℃ for 10 min, centrifuge at 12000 rpm for 10 min, and take the supernatant as PCR template.

c． Drug-resistant gene detection: Conduct PCR with drug resistance gene primers.

Take 5 μL PCR amplification products and initiate electrophoresis separately in 2% agarose gel. Each test will have negative and positive controls. Under the UV light, a bright band in the same location as the positive control sample indicates the presence of Amplification products.

c.1-tetracycline resistance plasmid tetM gene detection Primer design, PCR amplification detection.

c.2-Macrolides 23S rRNA gene

c. 3-Ribosomal protein gene L4

c.4-Ribosomal protein gene L22 gene

c. 5-Quinolones gyrA gene

V. Pilot Study

We will conduct a pilot study to evaluate feasibility and acceptability of the study. We will refine the study design based on the pilot research. Specifically, the pilot will evaluate possible harms arising from the study to the target group (such as self-reported drug side effects, psychological distress or difficulty in dealing with family relationship due to a positive result, and other unexpected harms), pretesting the questionnaire, understanding sample contamination between intervention and control group (ie. whether participants in the control group receive information distributed in the intervention group about chlamydia infection and adverse pregnancy outcomes, and request test and treatment afterwards), potential confounding factors (being classified as infectious diseases and non-infectious diseases factors), data collection process indicators, and required resources and budget. Solutions for problems identified, and refinement plan for the study and questionnaire will also be developed based on the pilot data. We intend to recruit a total of 200 pregnant women for the pilot study.

VI. Research Foundation

The Dermatology Hospital of Southern Medical University (Guangdong Provincial Dermatology Hospital/ Guangdong Provincial Centers for Skin Diseases and STD Control) plays a key role in STD/HIV control related research. It is a collaborator for many national research projects and

international projects such as the national-level program for comprehensive syphilis control (initiated in 2013), WHO HIV testing program, and program of prevention of mother-to- child transmission of syphilis starting in 2012. These valuable projects have generated compelling results that have driven regional and national policy development. Additionally, it has developed an experienced platform to conduct large epidemiology studies. Launched in 2008 as a collaboration between the Guangdong Provincial Dermatology Hospital and the University of North Carolina at Chapel Hill, UNC-South China STD Research training center (Training Center) is a department within the Guangdong Provincial STD Control Center. Until now, the training center has trained 13 postdoctoral fellows on HIV/STD control, resulting in 100 publications in the past four years. Each year, there are more than ten internationally renowned HIV and STD experts who teach and provide guidance for STD/HIV research.

For now, the Guangdong Provincial Centers for Skin Diseases and STD Control has the most complete STD control network in the nation. Specifically, it has 21 city-level control centers for STDs and 121 municipal and county-level control centers in charge of STD surveillance and prevention in Guangdong province. The STDs surveillance system of this center covers 1332 hospitals throughout the province: 6 national STD surveillance sites; 3 national STD clinical sites; 10 chlamydia/Gonorrhea surveillance sites for STD patients; 6 MSM STD surveillance sites; and 7 comprehensive syphilis control districts. The center has published 10 scientific papers in international journals, and 44 papers in Chinese journals.

Granted the *Guangdong STD Central Laboratory* by the Guangdong provincial health department in 2003, the unit currently has a comprehensive venereal disease laboratory center. This center is responsible for venereal disease prevention/treatment technical training and scientific research

throughout the province. As a tertiary standardized STD central laboratory of Guangdong province, the improved facility conditions, professional cell culture chamber, immunology laboratory, and molecular biology laboratory are equipped with Roche (lightcycler2.0) by real-time fluorescence quantitative PCR (Bio-Rad Power Pac 3000); Bole (Bio-Rad Power Pac 3000)Horizontal; electrophoresis Bole(Bio-Rad Power Pac 3000) vertical electrophoresis; The Capp hybrid instrument; (Thermo Revco) -80 C ultra-low temperature refrigerator; Bole (Bio-Rad Smart Spec Plus) nucleic acid / protein content determination apparatus; and other advanced instruments. The center has a variety of resources required for this project, ensuring the smooth implementation and completion of this project.

Guangzhou Women and Children's Medical Center (Guangzhou Woman & Infants Hospital, Guangzhou Maternal and Child Health Hospital, Children`s Hospital of Guangzhou, Guangzhou Woman & Infants Hospital) was founded in September 2006. It is integrated from the former Guangzhou Children's Hospital and Guangzhou Woman & Infants Hospital. The hospital has three key clinical specialties affiliated with the National Ministry of Health. There are seven Guangdong provincial key clinical specialties and subjects, and two Guangdong provincial 12th five-year Medical key laboratories; it is the base for the postdoctoral innovation practice of Guangdong Province, the teaching practice base for the Affiliated Hospital of Guangzhou Medical University, Zhongshan University, Southern Medical University, and the Graduate training base of Jinan University. The tertiary first class hospital, specialized for women and children, integrates prevention, medical care, health care, scientific research, and teaching. In 2016, the annual outpatient volume totaled 3761000 visits, 92919 of which were hospitalized patients and 22455 of which were childbirths.

Currently, the center is the implementation department for the Guangzhou birth cohort project (*Guangzhou Baby Plan*). The cohort has successfully recruited 30,000 pairs of mothers and children for regular follow- ups and systemically collected half a million specimens. Follow-up visit are regularly conducted at 6 weeks, 6 months, 1 year, 2 years, 3 years, and 6 years of age. Follow-ups are planned up until 18 years of age. The birth cohort -centered research platform for maternal and child health supports more than 20 major scientific research projects at the national, provincial and municipal level. It has accumulated over twenty million RMB (31,240,000 USD) for scientific research. Since January 2010, the project team has had 29 scientific publications in international journals and 40 papers in Chinese journals. Guangzhou Women and Children's Medical Center (Zengcheng Campus) is the largest women and children's medical center within the district. The center focuses on prevention, medical care, health care, scientific research and teaching. Soon, they will also implement the birth cohort research for pregnant women at Zengcheng.

In summary, the local collaboration institutions for this study have abundant experience conducting clinical and epidemiology research. They possess the skills and resources to monitor large clinical RCTs. The large birth cohort study in Guangzhou Women and Children's Medical Center and the experience of the Dermatology Hospital of Southern Medical University in STD research will help our project operate smoothly to achieve our final objectives.

VII. Quality Control

Clinician Training: The research team will invite the clinicians from Southern Medical University of Dermatology Hospital and Guangzhou Women and Children's Center to participate in a training course. The main training contents include: 1) the possible influence of genital

Chlamydia infection on pregnant women, fetuses and newborns 2) screening, diagnosis, treatment, and prognosis of chlamydial infection among pregnant women and 3) diagnosis and treatment of chlamydial conjunctivitis and pneumonia among neonates. The total training time will be 4 hours. Additionally, the research team will create a simple clinical manual which will distributed to the relevant clinicians for their reference.

Urine Sample Collection Staff Training: Laboratories from Guangdong Dermatology Hospital will provide training to urine sample collectors and demonstrate how to properly collect and store urine samples. The total training time will be 2 hours.

Questionnaire data entry: The research team will use Epidata, a data input software, to manage the questionnaire data. Two data processors will be responsible for dual entry to reduce input errors.

Clinical Data Audit: Three clinicians from Guangzhou Women and Children Medical Center will be responsible for verifying the diagnosis and treatment plans of patients and their children according to the international classification of diseases and diagnostic criteria.

VIII. Annual Plan

Task/Year	1st year	2nd year	3rd year	4th year	5th year
Study design, project propose and preparation					
Start pilot study to understand the disease prevalence among the target population					
Recruit participants\ baseline survey and collecting urine sample					
Randomization					
CT detection for intervention group					

patients and their partner CT treatment for intervention group					
primary report					
CT detection for control group					
patients and their partner CT treatment for control group					
Midterm report					
Follow up survey after delivery					
final report					
clinical data collecting					
Date input, management and analysis					
Manuscript writing and publishing					
Summary Report					

IX. References

1. Newman L, Rowley J, Vander Hoorn S, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. PLoS One 2015;**10**(12):e0143304 doi: 10.1371/journal.pone.0143304[published Online First: Epub Date]|.
2. Braxton J, Carey D, Davis DW, et al. Sexually transmitted disease surveillance 2014. 2015
3. Low N, Redmond S, Alexander K, et al. Chlamydia control in Europe: literature review. 2014
4. N L. Sexually Transmitted Infections in Primary Care 2013 (RCGP/BASHH), 2013.
5. Adachi K, Nielsen-Saines K, Klausner JD. Chlamydia trachomatis infection in pregnancy: the global challenge of preventing adverse pregnancy and infant outcomes in Sub-Saharan Africa and Asia. BioMed research international 2016;**2016**
6. Ryan GM, Abdella TN, McNeeley SG, et al. Chlamydia trachomatis infection in pregnancy and effect of treatment on outcome. American Journal of Obstetrics & Gynecology 1990;**162**(1):34-39
7. Martin DH, Eschenbach DA, Cotch MF, et al. Double-blind placebo-controlled treatment trial of Chlamydia trachomatis endocervical infections in pregnant women. Infectious diseases in obstetrics and gynecology 1997;**5**(1):10-17
8. Reekie J, Roberts C, Preen D, et al. Chlamydia trachomatis and the risk of spontaneous preterm birth, babies who are born small for gestational age, and stillbirth: a population-based cohort study. The Lancet Infectious Diseases doi: 10.1016/S1473-3099(18)30045-8[published Online First: Epub Date]|.
9. Reekie J, Roberts C, Preen D, et al. Chlamydia trachomatis and the risk of spontaneous preterm birth, babies who are born small for gestational age, and stillbirth: a population-based cohort study. The Lancet Infectious Diseases 2018
10. Novikova N, Cluver C. Interventions for treating genital Chlamydia trachomatis infection in pregnancy. The Cochrane Library 2013
11. Force RotUSPST. *The Guide to Clinical Preventive Services 2014*. Rockville (MD), 2014.

12. Ong J, Chen M, Hocking J, et al. Chlamydia screening for pregnant women aged 16–25 years attending an antenatal service: a cost-effectiveness study. BJOG: An International Journal of Obstetrics & Gynaecology 2016;**123**(7):1194-202
13. Honey E, Augood C, Templeton A, et al. Cost effectiveness of screening for Chlamydia trachomatis: a review of published studies. Sexually transmitted infections 2002;**78**(6):406-12
14. Chen X-S, Yin Y-P, Chen L-P, et al. Sexually transmitted infections among pregnant women attending an antenatal clinic in Fuzhou, China. Sexually transmitted diseases 2006;**33**(5):296-301
15. Luo Y, Jiang C, Liang T, et al. The birth weight of 590 infants and factors associated with low birth wegiht. Journal of Guangxi Medical University 2017;**34**(5):771-72
16. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. The Lancet 2016;**387**(10018):587-603
17. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet (London, England) 2016;**387**(10018):587-603 doi: 10.1016/s0140-6736(15)00837-5[published Online First: Epub Date]|.

X. Verification of Foreign Language Translation

Instructions: The Principal Investigator is responsible for ensuring that UNC-CH IRB-approved study documents, e.g., recruitment materials and consent forms, are accurately translated into a language understandable to study participants. If any study documents will be administered in languages other than English, the Principal Investigator must, as relevant:

- Submit this form with the initial application for IRB review.
- Submit this form if, as part of a study modification, there is a request to add new study documents that will be translated.
- Ensure that all translated documents are approved by the local IRB/Ethics Committee (EC) at the site(s) where the study will be performed, if any, prior to their use in the field.
- Submit the translated documents to the UNC-CH IRB as soon as they become available.

A. PROTOCOL INFORMATION	
☒ Initial Review ☐ Modification Request (to add new documents)	
IRB Study Number (if known)	**18-1168**
Study Title	**IGHID 11818 - Providing Genital Chlamydia Trachomatis Treatment to Pregnant Women to Prevent Adverse Pregnancy Outcomes: A Randomized Control Trial Pilot Study**
Principal Investigator	**Weiming Tang**

B. LIST OF DOCUMENTS TO BE TRANSLATED (attach additional pages as needed)

Document Name	Name(s) of Local Reviewing IRB/Ethics Committee (if any)	Translated Language(s)	Person Preparing Translation(s)	Name of Translator
ICF v2018-09-19	**Ethic Committee of Nanhai Hospital of Sountern Medical University**	**Chinese**	☐ UNC-CH PI ☐ Local Investigator ☐ Certified Translator ☒ Other, Specify: **Research Assistant**	**Xuewan Sun**

			☐ UNC-CH PI ☐ Local Investigator ☐ Certified Translator ☐ Other, Specify:	
			☐ UNC-CH PI ☐ Local Investigator ☐ Certified Translator ☐ Other, Specify:	
			☐ UNC-CH PI ☐ Local Investigator ☐ Certified Translator ☐ Other, Specify:	

C. Certification by Principal Investigator and Translator

By signing this form, I certify that I will fulfill my responsibility as Principal Investigator to ensure that IRB-approved study documents, e.g., recruitment materials and consent forms, are accurately translated in a language understandable to study participants.

_____ _____

Principal Investigator's Signature Date

By signing this form, I confirm that translations of the documents listed above will be accurate and complete.

Xuewan Sun 2020. 07. 02

_____

Translator's Signature Date